DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 356

[Docket No. 81N-0033]

Over-the-Counter Dental and Oral Health Care Drug Products for Antiplaque Use; Safety and Efficacy Review

AGENCY: Food and Drug Administration, HHS.

ACTION: Request for data and information.

SUMMARY: The Food and Drug Administration (FDA) is announcing a call-for-data for ingredients contained in products bearing antiplaque and antiplaque-related claims, such as "for the reduction or prevention of plaque, tartar, calculus, film, sticky deposits, bacterial build-up, and gingivitis." The agency will review the submitted data to determine whether these products are generally recognized as safe and effective and not misbranded for their labeled uses. This notice also describes the agency's general enforcement policy governing the marketing of over-the-counter (OTC) drug products bearing antiplaque and antiplaque-related claims during the pendency of this review. This request is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Data and information to be submitted by March 18, 1991.

ADDRESSES: Submissions should be sent to the Division of OTC Drug Evaluation (HFD-210), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

SUPPLEMENTARY INFORMATION: In 1972, FDA established the OTC drug review to evaluate drugs marketed OTC in the United States. The final regulations providing for the OTC drug review were published in the Federal Register of May 11, 1972 (37 FR 9464) (subsequently recodified at 21 CFR 330.10). The agency appointed 17 advisory review panels to evaluate the safety and effectiveness data submitted on active ingredients found in OTC drug products. Two advisory review panels, the advisory Review Panel on OTC Dentifrice and Dental Care Drug Products (Dental Panel) and the Advisory Review Panel on OTC Oral Cavity Drug Products (Oral Cavity Panel), reviewed OTC dental and oral health care drug products. In a Federal Register notice published on January 30, 1973, interested persons were invited to submit data to support the stated claims for dentrifices and dental care agents (38 FR 2781).

The Dental Panel (which deliberated from 1973 to 1978) reviewed fluoride dentifrices which contain abrasive ingredients. However, this Panel was

primarily concerned about the effect of fluoride on dental caries and did not specifically consider the activity of abrasives for the removal of plaque. In its report on OTC anticaries drug products (published in the Federal Register of March 28, 1980; 45 20668), the Dental Panel did acknowledge that the cleansing function of a dentrifrice is achieved by the mechanical removal of dental plaque, stain, and debris from tooth surfaces by the abrasive system (45 FR 20676). Because there were no submissions from drug companies for dental products making antiplaque claims in their labeling at that time, there was no need for the Dental Panel to consider the particular abrasives in dentifrices as active ingredients for the removal of plaque.

The Dental Panel did consider gingivitis and antiplaque claims for dentifrices in its report on OTC oral mucosal injury drug products (published in the Federal Register of November 2, 1979; 44 FR 63270). Claims for the prevention, control, or treatment of gingivitis were placed in Category II (44 FR 63283). The Dental Panel concluded that "drug products which have antiplaque, plaque control, or gingivitis claims are not currently appropriate for the OTC market because there is no general recognition of any such drug products as safe and effective for these indications at this time." The Dental Panel recommended that such drug products and claims should be evaluated by FDA through the new drug application (NDA) procedures.

The Oral Cavity Panel (which deliberated from 1974 to 1979) only reviewed antimicrobial ingredients for sore mouth and sore throat claims and did not specifically evaluate the effectiveness of oral health care antimicrobial agents to inhibit plaque formation. (See the Federal Register of May 25, 1982; 47 FR 22760.) Although data on plaque reduction as a measure of the effectiveness of antimicrobial ingredients were presented to the Oral Cavity Panel, the Panel did not accept such data because it believed that "the rationality of plaque reduction as a criterion of effectiveness of antimicrobial agents for use in the mouth and throat is highly debatable, and evidence of the validity of the method is scant" (47 FR 22840). Because the Oral Cavity Panel was not charged with reviewing drug products used to treat dental or periodontal diseases, it did not specifically consider ingredients with antiplaque claims.

The Dental Panel described dental plaque as a gel-like mat that is firmly attached to the surface of a tooth or restoration. The Panel stated that plaque is made up of microbial masses, intermicrobial matrix, and nonbacterial cellular inclusions (45 FR 20668 at 20671). The Oral Cavity Panel described plaque as a soft and tenacious material found on the surfaces of teeth. It added that the composition of plaque is multivaried, and its microbial and biochemical composition varies with the site of formation, the duration of accumulation, the composition of the diet, and perhaps, other undetermined factors (47 FR 22780 at 22841). Studies have demonstrated that the presence of dental plaque is directly related to the occurrence of gingivitis in humans (Refs. 1 and 2).

Dorland's Illustrated Medical Dictionary (Ref. 3) defines dental plaque as "a soft, thin film of food debris, mucin, and dead epithelial cells deposited on the teeth, providing the medium for the growth of various bacteria." Dorland's states that plaque "plays an important etiologic role in the development of dental caries and

periodontal and gingival diseases." [Ref. 3].

Section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act (the act) [21 U.S.C. 321(g)(1)] defines a "drug" primarily as an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease or an article intended to affect the structure or function of the body. Section 201(i) of the act [21 CFR 321(i)] defines a "cosmetic" essentially as an article applied to the human body for "cleansing, beautifying, promoting attractiveness, or altering the appearance." Products may be simultaneously drugs and cosmetics. Because plaque is a colorless bacterial layer which is not clearly visible unless calcified or stained, plaque removal is not considered a cosmetic purpose. Plaque-reduction or removal is intended to prevent disease, i.e., gingivitis, caries, and periodontal disease. Primarily because of this explicit or implicit disease prevention purpose regarding plaque, the agency considers plaque reduction and removal claims to be drug claims.

Two classes of dental and oral health care products have made antiplaque claims over the years: (1) Products containing abrasives that rely on mechanical action to remove plaque, and (2) products that claim to reduce or remove plaque by antimicrobial or chemical activity. Because such claims are drug claims, the safety and effectiveness of ingredients used in products making plaque reduction and removal claims must be demonstrated.

Recently, products with antiplaque claims have been heavily promoted, and the agency is aware that a great deal of research has been conducted in this area in recent years. Because neither the Dental Panel nor the Oral Cavity Panel reviewed in detail the safety and effectiveness data on particular ingredients for antiplaque or gingivitis indications, the agency has determined that it is appropriate to issue another call-for-data on such ingredients. Historically, claims such as "for the reduction or prevention of plaque, tartar, calculus, film, sticky deposits, bacterial build-up, and gingivitis" have been made for dental products primarily in promotional materials and advertising, including professional labeling and advertising (information provided to health professionals but not to the general public). Some of these claims, such as plaque removal claims, have appeared on the labeling of certain OTC drug products marketed to the general public. Other claims, such as "for the reduction, prevention, or treatment of gum disease, inflamed gums, swollen gums, bleeding gums, pyorrhea, Vincent's infection, periodontal disease, or tooth-destroying acids," as well as "promote healthy gums" or to "condition gums" have also appeared in promotional material, advertising, and profesional labeling for dental products. Although the agency questions the acceptability of some of these claims for an OTC drug product, the agency will accept data on such claims in this review in order to make a determination as to their status. The agency invites comment on the appropriateness of each such claim for OTC drug labeling. (See general regulatory policy discussed below.)

FDA invites the submission of data, published and unpublished, and any other information pertinent to active ingredients used in any dosage forms of dental and oral health care drug products, such as dentifrices, gargles, mouthwashes, and similar products that have antiplaque or antiplaque-related claims. In order to be eligible for review under the OTC drug review procedures, the ingredient must have been marketed in a product with the relevant indication (e.g., with a plaque or gingivitis claim) to a material extent and for a material time (21 U.S.C. 321(p)(2)). Manufacturers of products bearing antiplaque and antiplaque-related claims that contain active ingredients that have not been marketed for such indication(s) to a material extent and for a material time should submit supporting safety and effectiveness data in an NDA. These products may not be legally marketed in interstate commerce until an NDA is approved.

Manufacturers of products bearing antiplaque and antiplaque-related that contain active ingredients that have been marketed for such indication(s) to a material extent and for a material time may submit supporting safety and effectiveness data to the OTC drug reveiw. The submission of data should include information that demonstrates that the ingredients have been marketed to a material extent and for a material time for the relevant indications(s). Products with ingredients under consideration for these indications in the OTC drug review may be marketed (at the same dosage strength and in the same dosage form) under the manufacturer's good faith belief that the product is generally recognized as safe and effective and not misbranded and in accordance with FDA's enforcement policies related to the OTC drug review. (*See* FDA's Compliance Policy Guides Nos. 7132b.15 and 7132b.16.) Such products are marketed at the risk that the agency may adopt a position requiring relabeling, recall, or other regulatory action.

This call-for-data is part of the agency's ongoing review of OTC oral health care drug products. The Oral Cavity Panel's report was published in the Federal Register of May 25, 1982 (47 FR 22760). The agency is issuing the tentative final monograph for OTC oral health care drug products in several segments. The first segments addressed OTC oral health care anesthetic/analgesic, astringent, debriding agent/oral wound cleanser, and demulcent drug products and was published in the Federal Register of January 27, 1988 (53 FR 2438). An amendment to this segment will address OTC relief of oral discomfort drug products. Another segment will contain the agency's responses to comments regarding oral health care antimicrobial drug products and comments on the drug or cosmetic status of certain oral health care products and claims. These segments will be published in future issues of the Federal Register. This call-for-data is the initial step in the development of the final segment of the rulemaking for OTC oral health care drug products, which will address antiplaque and antiplaque-related claims.

To be considered in this view, eight copies of the data and information must be submitted, preferably bound, indexed, and on standard size paper (approximately 8½ by 11 inches). The agency suggests that all submissions be in the format described in 21 CFR 330.10(a)(2).

In accordance with § 330.10(a)(2), all submitted data on antiplaque ingredients and claims will be handled as confidential by the agency. However, all the submitted information will be put on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, 30 days after publication of any proposed rules resulting from the review of the submitted material, except to the extent that the person submitting it demonstrates that it falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the act (21 U.S.C. 331(j)). At the time of publication, requests for confidentiality should be submitted to William E. Gilbertson, Center for Drug Evaluation and Research (HFD-210) (address above).

Data and information should be addressed to the Division of OTC Drug Evaluation (address above) Data submitted after the closing date of March 18, 1991 will not be considered except by petition pursuant to § 10.30 (21 CFR 10.30).

In the Federal Register of December 19, 1988 (53 FR 50940), the agency announced the establishment of the Dental Products Panel and stated that this panel will function at times as an OTC drug advisory panel to review and evaluate various currently marketed nonprescription drug products for human use and the adequacy of their labeling. The panel will advise the Commissioner of Food and Drugs on the promulgation of mongraphs establishing conditions under which these drugs are generally recognized as safe and effective and not misbranded. The agency intends to use this panel to review and evaluate ingredients contained in products bearing antiplaque and antiplaque-related claims prusuant to this call-for-data.

References

(1) Loe, H., E. Theilade, and S.B. Jensen, "Experimental Gingivitis in Man," *Journal of Periodontology*, 36:177-187, 1965.

(2) Theilade, E., et al., "Experimental Gingivitis in Man II. A Longitudinal Clinical and Bacteriological Investigation," *Journal of Periodontal Research*, 1:1-13, 1966.

(3) "Dorland's Illustrated Medical Dictionary," 27th Ed., W.B. Saunders Co., Philadelphia, 1988, s.v. "plaque."

Dated: September 12, 1990.

Ronald G. Chesemore,

Associate Commissioner for Regulatory Affairs.

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